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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/007,459	11/07/2001	David L. Lewis	Mirus.030.04	3774

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MIRUS CORPORATION
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EXAMINER	
GIBBS, TERRA C	
ART UNIT	**PAPER NUMBER**
1635	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	04/24/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/007,459	LEWIS ET AL.	
	Examiner	Art Unit	
	Terra C. Gibbs	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 April 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *11 and 13-18* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *11 and 13-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office Action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission mailed on April 12, 2007 has been entered.

Claim 11 has been amended.

Claims 11 and 13-18 are pending in the instant application.

Claims 11 and 13-18 have been examined on the merits.

Response to Arguments

Applicants Amendment and Response filed April 12, 2007 have been considered. Rejections and/or objections not reiterated from the previous Office Action mailed January 29, 2007 are hereby withdrawn. Any arguments addressing said rejections and/or objections are moot. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 11, 13, 14, 16, and 17 are rejected under 35 U.S.C. 102(b) as being anticipated by Desjardins et al. (Journal of Pharmacology and Experimental Therapeutics, 1996 Vol. 278:1419-1427).

Claim 11 is drawn to a process for inhibiting the expression of a gene in an *in vivo* parenchymal cell in a target tissue in a mammal comprising, mixing a double stranded RNA and an amphipathic compound to form a complex wherein the zeta potential of the complex is less negative than the zeta potential of the double strand RNA alone; injecting a volume of a solution containing the complex into an efferent or afferent mammalian vessel of the target tissue *in vivo*, wherein the rate of injection and the volume of the solution increase permeability of a vessel within the target tissue thereby delivering the double strand RNA oligonucleotide from inside the vessel, through a wall of the vessel, into the extravascular space and into the *in vivo* parenchymal cell, wherein the double strand oligonucleotide inhibits expression of the gene. Claims 13, 14, 16, and 17 depend from claim 11 and include all the limitations of claim 11 with the further limitations wherein increasing the permeability of the vessel consists of increasing pressure against vessel walls; wherein the parenchymal cell is selected from liver cells, heart cells, and kidney cells; wherein the complex has a

negative charge; and wherein increasing the pressure consists of increasing volume of fluid within the vessel.

It is noted that the instant specification does not define the term, "target tissue". Therefore, the Examiner is interpreting this term broadly to include any tissue, but more specifically the site of injection. It is also noted that the instant specification at page 5, last paragraph discloses, "Permeability is defined here as the propensity for macromolecules such as polynucleotides to move through vessel walls and enter the extravascular space".

Desjardins et al. disclose the pharmacokinetics of a synthetic, chemically modified hammerhead ribozyme against the rat cytochrome P-450 3A2 mRNA after single intravenous injections (see Abstract). Specifically, Desjardins et al. disclose that a CYP3A2 hammerhead ribozyme, dissolved in a sterile, pyrogen-free isotonic saline solution, was injected into the jugular vein of adult male Sprague-Dawley rats via an access catheter (see page 1421, second column). Desjardins et al. disclose that the injection volume was 0.25 mg/rat (see page 1421, at Dosage Form). Desjardins et al. disclose that following injection, the ribozyme was detected in plasma, kidney, liver, and brain (see Abstract, Figure 2, and discussion at page 1423). It is noted that, given the definition of "Permeability" in the instant specification as discussed above, the Examiner is interpreting that the 0.25 mg/rat injection volume increased permeability within the target tissue since the ribozyme complex moved through the vessel walls of the jugular vein and entered the plasma (e.g. extravasuclar space). It is also noted that the Examiner is of the opinion that following injection, the ribozyme complex increased

pressure against the vessel walls since the access catheter itself is external to the vessel. The Examiner is also interpreting the sterile, pyrogen-free isotonic saline ribozyme solution to be an amphipathic solution; the jugular vein to be a vessel; the plasma to be the extravascular space; and either the kidney, liver, or brain to be an *in vivo* parenchymal cell. It is further noted that Desjardins et al. disclose that the ribozyme bound to human serum albumin in a microbubble assay (see page 1422, first column and Table 1). Given the microbubble assay results, the Examiner is interpreting that the ribozyme complex had a net negative charge.

It is noted that Desjardins et al. are silent regarding whether the zeta potential of the sterile, pyrogen-free isotonic saline ribozyme solution is less negative than the zeta potential of the ribozyme alone. However, the burden of establishing whether the prior art sterile, pyrogen-free isotonic saline ribozyme solution has the function of exhibiting zeta potential less negative than the zeta potential of the ribozyme alone, under generally any assay conditions falls to Applicant. See MPEP 2112.01, "Where the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a prima facie case of either anticipation or obviousness has been established. *In re Best*, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977). "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." In re Spada, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). Therefore, the prima facie case can be rebutted by evidence showing that the prior art products do not necessarily possess the

characteristics of the claimed product. In re Best, 562 F.2d at 1255, 195 USPQ at 433." See also MPEP 2112: "[T]he PTO can require an Applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his [her] claimed product." The MPEP at 2112 citing *In re Fitzgerald* 205 USPQ 594. 596, (CCPA 1980), quoting In re Best 195 USPQ 430 as per above. Therefore, it falls to Applicant to determine and provide evidence that the sterile, pyrogen-free isotonic saline ribozyme solution disclosed by Desjardins et al. would or would not have the additional functional limitation of exhibiting zeta potential less negative than the zeta potential of the ribozyme alone, as instantly claimed.

It is also noted that Desjardins et al. are silent regarding whether the injected chemically modified hammerhead ribozyme against the rat cytochrome P-450 3A2 inhibited gene expression. However, the burden of establishing whether the prior art chemically modified hammerhead ribozyme against the rat cytochrome P-450 3A2 has the function of inhibiting gene expression, under generally any assay conditions falls to Applicant. See MPEP 2112.01, "Where the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a prima facie case of either anticipation or obviousness has been established. *In re Best*, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977). "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." In re Spada, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). Therefore, the prima facie case can be rebutted by evidence showing that the

prior art products do not necessarily possess the characteristics of the claimed product. In re Best, 562 F.2d at 1255, 195 USPQ at 433." See also MPEP 2112: "[T]he PTO can require an Applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his [her] claimed product." The MPEP at 2112 citing *In re Fitzgerald* 205 USPQ 594. 596, (CCPA 1980), quoting In re Best 195 USPQ 430 as per above. Therefore, it falls to Applicant to determine and provide evidence that the chemically modified hammerhead ribozyme against the rat cytochrome P-450 3A2 disclosed by Desjardins et al. would or would not have the additional functional limitation of inhibiting gene expression, as instantly claimed.

Therefore, absent evidence to the contrary, Desjardins et al. anticipate claims 11, 13, 14, 16, and 17.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 11 and 13-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zimmer, A. (Methods, 1999 Vol. 18:286-295, made of record in the previous Office Action mailed August 24, 2005) in view of Vaish et al. (Nucleic Acids Research, 1998 Vol. 26:5237-5242, made of record in the previous Office Action mailed July 25, 2006), and Zhang et al. (Human Gene Therapy, 1999 Vol. 10:1735-1737, made of record in the previous Office Action mailed August 24, 2005).

Claim 11 is drawn to a process for inhibiting the expression of a gene in an *in vivo* parenchymal cell in a target tissue in a mammal comprising, mixing a double stranded RNA and an amphipathic compound to form a complex wherein the zeta potential of the complex is less negative than the zeta potential of the double strand RNA alone; injecting a volume of a solution containing the complex into an efferent or afferent mammalian vessel of the target tissue *in vivo*, wherein the rate of injection and the volume of the solution increase permeability of a vessel within the target tissue thereby delivering the double strand RNA oligonucleotide from inside the vessel, through a wall of the vessel, into the extravascular space and into the *in vivo* parenchymal cell, wherein the double strand oligonucleotide inhibits expression of the gene. Claims 13-18 depend from claim 11 and include all the limitations of claim 11 with the further limitations, wherein increasing the permeability of the vessel consists of increasing pressure against vessel walls; wherein the cell is a liver cell; wherein the complex has a positive or negative charge; wherein increasing the pressure consists of increasing volume of fluid within the vessel; and wherein the solution is inserted within 2 minutes.

It is noted that the instant specification does not define the term, "target tissue". Therefore, the Examiner is interpreting this term broadly to include any tissue, but more specifically the site of injection. It is also noted that the instant specification at page 5, last paragraph discloses, "Permeability is defined here as the propensity for macromolecules such as polynucleotides to move through vessel walls and enter the extravascular space".

Zimmer teach delivering an antisense oligonucleotide complexed with positive and negative charged polymers into a liver cell via tail vein injection (see Abstract and discussion at page 292). Specifically, Zimmer teach mixing an antisense and a polymer, wherein the zeta potential of the complex is less negative than the zeta potential of the antisense alone (see Table 2 and page 290, first full paragraph, which states, "at a lower ratio the surface charge of the nanoparticles is decreased by the ODNs as indicated by a decreased ζ potential"). Zimmer teach Protocol A, which provides cationically (positively) charged oligonucleotide-loaded nanoparticles and Protocol B, which provides anionically (negatively) oligonucleotide-loaded nanoparticles (see page 287, first and second paragraphs). It is noted that Zimmer et al. teach that the antisense nanoparticle complexes were injected into the tail vein at 5 nmol/5 ml/kg. It is noted that, given the definition of "Permeability" in the instant specification as discussed above, the Examiner is interpreting that the 5 nmlo/5 ml/kg injection volume increased permeability within the target tissue since the ribozyme complex moved through the vessel walls of the jugular vein and entered the extravasuclar space, ultimately reaching the liver. It is also noted that that the Examiner is of the opinion that

the pressure against the vessel walls would inherently be increased because the needle used to deliver the oligonucleotide complexed with positive and negative charged polymers is external to the tail vein. The Examiner is also interpreting the tail vein to be the vessel, where the oligonucleotide obviously traveled from inside the vessel into the extravascular space to finally reach the liver cell.

It is noted that Zimmer et al. are silent regarding whether or not the antisense oligonucleotide complexed with positive and negative charged polymers delivered into liver cells via tail vein injection inhibited expression of a target gene. However, the burden of establishing whether the prior art antisense oligonucleotide complexed with positive and negative charged polymers has the function of inhibiting gene expression, under generally any assay conditions falls to Applicant. See MPEP 2112.01, "Where the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a prima facie case of either anticipation or obviousness has been established. *In re Best*, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977). "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." In re Spada, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). Therefore, the prima facie case can be rebutted by evidence showing that the prior art products do not necessarily possess the characteristics of the claimed product. In re Best, 562 F.2d at 1255, 195 USPQ at 433." See also MPEP 2112: "[T]he PTO can require an Applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his [her] claimed

product." The MPEP at 2112 citing *In re Fitzgerald* 205 USPQ 594. 596, (CCPA 1980), quoting In re Best 195 USPQ 430 as per above. Therefore, it falls to Applicant to determine and provide evidence that the antisense oligonucleotide complexed with positive and negative charged polymers taught by Zimmer et al. would or would not have the additional functional limitation of inhibiting expression of a target gene, as instantly claimed.

Zimmer do not teach a double stranded RNA or inserting a dsRNA into a cell of a mammal within 2 minutes.

Vaish et al. teach that antisense oligonucleotides and ribozymes are two approaches that use similar techniques to achieve the same goal (see page 5239, first column). For example Vaish et al. teach, "The first step for inhibition of gene expression by a ribozyme is its binding to the mRNA. This step is akin to the antisense oligodeoxynucleotide method (AS-ODN) used for the same purpose. It is, therefore, not surprising that both approaches benefit from experience in each others areas".

Zhang et al. teach that the tail vein injection of naked plasmid DNA enables foreign gene expression in the liver (see Abstract). Zhang et al. also teach maximal gene expression was achieved when the DNA solution was injected within 7-120 seconds (see Figure 1, injection speed). Zhang et al. conclude that the rapid injection of plasmid DNA has great potential for a wide variety of laboratory studies.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of filing to devise a process for inhibiting the expression of a gene in an *in vivo*

parenchymal cell in a target tissue in a mammal using the methods taught by Zimmer et al.

One of ordinary skill in the art would have been motivated to devise a process for inhibiting the expression of a gene in an *in vivo* parenchymal cell in a target tissue in a mammal for the purpose of nucleic acid gene therapy. One of ordinary skill in the art would have been motivated to substitute the antisense nucleic acid as taught by Zimmer with the dsRNA as instantly claimed since Vaish et al. teach a dsRNA would have been considered to be structurally equivalent to an antisense since both are sequence specific nucleic acid inhibitors of gene expression, which are used for the same purpose. Further, see MPEP 2144.06. It would have been obvious to one of ordinary skill in the art to insert the complex within 2 minutes since Zhang et al. taught maximal nucleic acid expression by tail vein injection is achieved when DNA solutions are injected within 7-120 seconds.

One would have had a reasonable expectation of success at devising a process for inhibiting the expression of a gene in an *in vivo* parenchymal cell in a target tissue in a mammal because Zimmer clearly teach the successful delivery of an antisense nucleic acid to a liver cell and since antisense and dsRNA are both sequence specific nucleic acid inhibitors of gene expression and are art-recognized functional and structural equivalents, the instant invention would have been *prima facie* obvious to one of ordinary skill in the art at the time of filing.

Therefore, the invention would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Response to Arguments

It is noted that a similar rejection was made of record in the previous Office Action mailed July 25, 2006. It is further noted that this same rejection was maintained in the Office Action mailed on January 29, 2007. In response to this rejection, Applicants are of the opinion that the amendment to the claims obviates the instant rejection.

Applicant's arguments have been fully considered but are not found persuasive because contrary to Applicant's opinion, as detailed above, using the teachings of Zimmer et al. and Zhang et al., and the motivation of Vaish et al., the invention would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was filed.

Conclusion

No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Terra C. Gibbs whose telephone number is 571-272-0758. The examiner can normally be reached on 9 am - 5 pm M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Schultz can be reached on 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for

published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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tcg
April 21, 2007